AUSTRALIAN PATENT PUBLICATION

Application Number AU199514852B2
Patent Number AU707119B2

Title	Method for stabilizing pranoprofen and stable liquid preparation of pranoprofen
Classification(s)	A61K031/44
Application Number	AU199514852B2
Priority Data	JP 6-44184 (1994-03-15)
Filing Date	1995-03-15
Publication Date	1995-09-21
Publication Journal Date	1995-09-21
Accepted Journal Date	1999-07-01
Applicant(s)	Senju Pharmaceutical Co, Ltd
Inventor(s)	Koji Doi ; Hisako Sawa ; Yoshie Ozaki ; Yoshiyuki Kimura
Agent(s)	GRIFFITH HACK,GPO Box 4164,SYDNEY NSW 2001
Related Art	US 4525348 ; US 5032392 ; EP 0471084

AU9514852

(12) PATENT ABSTRACT (11) Document No. AU-A-14852/95
(19) AUSTRALIAN PATENT OFFICE

(54) Title
METHOD FOR STABILIZING PRANOPROFEN AND STABLE LIQUID PREPARATION OF PRANOPROFEN

(51)[6] International Patent Classification(s)
A61K 031/44

(21) Application No. : **14852/95** (22) Application Date : **15.03.95**

(30) Priority Data

(31) Number	(32) Date	(33) Country
6-44184	15.03.94	JP JAPAN

(43) Publication Date : **21.09.95**

(71) Applicant(s)
SENJU PHARMACEUTICAL CO, LTD

(72) Inventor(s)
KOJI DOI; HISAKO SAWA; YOSHIE OZAKI; YOSHIYUKI KIMURA

(74) Attorney or Agent
GRIFFITH HACK & CO., GPO Box 4164, SYDNEY NSW 2001

(57)

A method for stabilizing pranoprofen, comprising placing an aqueous solution of pranoprofen in coexistence with an antioxidant, or placing an aqueous solution of pranoprofen under the conditions of limited supply of oxygen, and a stable aqueous preparation of pranoprofen, comprising pranoprofen and an antioxidant. According to the present invention, the decomposition of pranoprofen in an aqueous solution of pranoprofen is remarkably suppressed. In particular, pranoprofen becomes stable to light, thus permitting long-term preservation of an aqueous solution, specifically a liquid preparation, of pranoprofen.

ABSTRACT OF THE DISCLOSURE

A method for stabilizing pranoprofen, comprising placing an aqueous solution of pranoprofen in coexistence with an antioxidant, or placing an aqueous solution of pranoprofen under the conditions of limited supply of oxygen, and a stable aqueous preparation of pranoprofen, comprising pranoprofen and an antioxidant. According to the present invention, the decomposition of pranoprofen in an aqueous solution of pranoprofen is remarkably suppressed. In particular, pranoprofen becomes stable to light, thus permitting long-term preservation of an aqueous solution, specifically a liquid preparation, of pranoprofen.

P/00/011
Regulation 3.2

AUSTRALIA

Patents Act 1990

ORIGINAL

COMPLETE SPECIFICATION

STANDARD PATENT

Invention Title: METHOD FOR STABILIZING PRANOPROFEN AND STABLE LIQUID PREPARATION OF PRANOPROFEN

The following statement is a full description of this invention, including the best method of performing it known to us:

GH&CO REF: P21942-L:ADK:RK

SPECIFICATION

METHOD FOR STABILIZING PRANOPROFEN AND STABLE LIQUID PREPARATION OF PRANOPROFEN

FIELD OF THE INVENTION

The present invention relates to a method for stabilizing pranoprofen having anti-inflammatory activity, in an aqueous solution of pranoprofen, and to a liquid preparation comprising, as an active ingredient, pranoprofen which is stabilized by adding an antioxidant.

BACKGROUND OF THE INVENTION

Pranoprofen having a chemical name of α-methyl-5H-[1]benzopyrano[2,3-b]pyridine-7-acetic acid exhibits prominent anti-inflammatory action, analgesic action and antipyretic action. It is a non-steroidal anti-inflammatory drug having a wider safety margin, and is commercially available by the product name of Niflan (trademark). The properties and production method thereof are described in United States Patent No. 3931295.

There has also been proposed an eye drop containing pranoprofen as an anti-inflammatory active ingredient and boric acid as an isotonizing agent, as being useful for, in particular, herpesvirus eye diseases (US Patent No. 4,607,038).

However, pranoprofen is unstable in an aqueous solution state (particularly to light) and is gradually decomposed during long-term preservations.

It is therefore an object of at least a preferred

embodiment of the present invention to provide a method for stabilizing pranoprofen in an aqueous solution state.

Another object of at least a preferred embodiment of the present invention is to provide an aqueous solution of pranoprofen, wherein decomposition of pranoprofen is suppressed.

According to the present invention, it has now been found that decomposition of pranoprofen can be markedly suppressed by placing an aqueous solution of pranoprofen in coexistence with an antioxidant, or placing an aqueous solution of pranoprofen under the conditions of limited supply of oxygen.

That is, the present invention and preferable modes thereof are as follows.

(1) A method for stabilizing pranoprofen, comprising placing an aqueous solution of pranoprofen in coexistence with an antioxidant.

(2) A method for stabilizing pranoprofen according to (1), comprising adding an antioxidant to an aqueous solution of pranoprofen.

(3) A method for stabilizing pranoprofen according to (2), wherein the weight ratio of the antioxidant to pranoprofen is 0.0002-5.0:1.

(4) A method for stabilizing pranoprofen according to (1), comprising sealing an aqueous solution of pranoprofen in a container formed from a mixture comprising a material for the container and an antioxidant.

(5) A method for stabilizing pranoprofen according to (4),

wherein the weight ratio of the antioxidant to the material is 0.0001-0.005:1.

(6) A method for stabilizing pranoprofen according to (4), wherein the container is made of polypropylene.

(7) A method for stabilizing pranoprofen according to (2), wherein the antioxidant is at least one compound selected from the group consisting of alkylphenols, benzopyran derivatives, sodium thiosulfate and amino acids.

(8) A method for stabilizing pranoprofen according to (7), wherein the alkylphenol is at least one compound selected from the group consisting of dibutylhydroxytoluene and butylhydroxyanisole.

(9) A method for stabilizing pranoprofen according to (7), wherein the benzopyran derivative is at least one member selected from the group consisting of L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] and salts thereof.

(10) A method for stabilizing pranoprofen according to (7), wherein the amino acid is at least one member selected from the group consisting of methionine, tryptophan and histidine.

(11) A method for stabilizing pranoprofen according to any one of (4)-(6), wherein the antioxidant is at least one alkylphenol.

(12) A method for stabilizing pranoprofen according to (11), wherein the alkylphenol is at least one member selected from the group consisting of dibutylhydroxytoluene and

butylhydroxyanisole.

(13) A method for stabilizing pranoprofen, comprising placing an aqueous solution of pranoprofen under the conditions of limited supply of oxygen.

(14) A method for stabilizing pranoprofen according to (13), comprising sealing a container, in which an aqueous solution of pranoprofen has been sealed, in a container or enclosing the container with a sheet, together with a deoxygenating agent.

(15) A method for stabilizing pranoprofen according to (13), comprising sealing an aqueous solution of pranoprofen in a container having a low oxygen permeability or enclosing the solution with a sheet having a low oxygen permeability.

(16) A stabilizing method according to (1), wherein the aqueous solution of pranoprofen is an eye drop or a collunarium.

(17) A stabilizing method according to (13), wherein the aqueous solution of pranoprofen is an eye drop or a collunarium.

(18) A stable liquid preparation of pranoprofen, comprising pranoprofen and an antioxidant.

(19) The liquid preparation of (18), wherein the antioxidant is at least one compound selected from the group consisting of alkylphenols, benzopyran derivatives, sodium thiosulfate and amino acids.

(20) The liquid preparation of (19), wherein the alkylphenol is at least one member selected from the group consisting of dibutylhydroxytoluene and butylhydroxyanisole.

(21) The liquid preparation of (19), wherein the benzopyran

derivative is at least one compound selected from the group consisting of L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] and salts thereof.

(22) The liquid preparation of (19), wherein the amino acid is at least one member selected from the group consisting of methionine, tryptophan and histidine.

(23) The liquid preparation of (18), wherein the weight ratio of the antioxidant to pranoprofen is 0.0002-5.0:1.

(24) The liquid preparation of (18), which is an eye drop.

(25) The liquid preparation of (18), which is a collunarium.

The first mode of the stabilizing method of the present invention is placing an aqueous solution of pranoprofen in coexistence with an antioxidant, which is realized by, for example, (i) adding an antioxidant to an aqueous solution of pranoprofen (Mode I) or (ii) sealing an aqueous solution of pranoprofen in a container formed from a mixture comprising a material for the container and an antioxidant (Mode II). The Modes I and II may be used in combination.

The antioxidant to be used in Mode I includes, for example, alkylphenols, benzopyran derivatives, sodium thiosulfate and amino acids.

Examples of alkylphenol include dibutylhydroxytoluene (BHT), butylhydroxyanisole (BHA), n-propyl gallate and catechol, with preference given to BHT and BHA.

Examples of benzopyran derivative include tocopherol, tocol, L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] and salts thereof, with preference given to L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] potassium salt (EPC-K_1).

Amino acid is, for example, methionine, tryptophan or histidine, with preference given to methionine and tryptophan.

When an antioxidant is added to an aqueous solution of pranoprofen according to Mode I, the weight ratio of the antioxidant to pranoprofen is generally 0.0002-5.0:1, preferably 0.002-2.5:1.

When an aqueous solution of pranoprofen is sealed in a container formed from a mixture comprising a material for the container and an antioxidant, according to Mode II, the material for the container is exemplified by those generally used for plastic containers, such as polyolefin [e.g. polyethylene (PE) and polypropylene (PP)], with preference given to PP.

The mixture for the container comprises a material for the container and an antioxidant. The weight ratio of the antioxidant to the material is, for example, 0.0001-0.005:1, preferably 0.0005-0.005:1.

In the Mode II, the antioxidant to be used is, for example, a phenol such as alkylphenol, alkyldiphenol or thiobisalkylphenol.

Examples of alkylphenol include dibutylhydroxytoluene

(BHT), butylhydroxyanisole (BHA), n-propyl gallate, stearyl ß-(3,5-di-t-butyl-4-hydroxyphenyl)propionate, tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionyloxymethyl]methane, 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1H,2H,3H-triazine-2,4,6-trione, 1,3,5-tris[(3,5-di-tert-butyl-4-hydroxybenzyl)-2,4,6-trimethyl]benzene and 3,9-bis[2-(3-(3-tert-butyl-4-hydroxy-5-methylphenyl)propionyloxy)-1,1-dimethylethyl]-2,4,8,10-tetraoxaspiro[5.5]undecane, with preference given to BHT and BHA.

Examples of alkyldiphenol include 2,2'-methylenebis(4-methyl-6-tert-butylphenol), 4,4'-butylidenebis(2-tert-butyl-5-methylphenol) and 2-tert-butyl-6-(3-tert-butyl-2-hydroxy-5-methylbenzyl)-4-methylphenyl acrylate.

Examples of thiobisalkylphenol include 4,4'-thiobis(2-tert-butyl-5-methylphenol).

The second mode of the stabilizing method of the present invention is placing an aqueous solution of pranoprofen under the conditions of limited oxygen supply. For example, a container containing an aqueous solution of pranoprofen sealed therein is sealed in another container or enclosed with a sheet in coexistence with a deoxygenating agent (Mode III), or an aqueous solution of pranoprofen is sealed in a container having a low oxygen permeability, or enclosed with a sheet having a low oxygen permeability (Mode IV).

In the Mode III, the container for sealing an aqueous solution of pranoprofen is subject to no particular limitation

as long as it can seal an aqueous solution of pranoprofen, and is preferably exemplified by a container formed from a mixture comprising a material for the container and an antioxidant, such as those exemplified for the above-mentioned Mode II, and a container having a low oxygen permeability to be mentioned below.

The deoxygenating agent to be used in Mode III is exemplified by iron powder, iron oxide, ascorbic acid and catechol, with preference given to iron oxide. The deoxygenating agent is preferably packed in a bag etc. made of an oxygen-permeable material and put to use.

The container and the sheet to enclose a container, in which an aqueous solution of pranoprofen has been sealed, together with a deoxygenating agent according to Mode III, are not subject to any particular limitation as long as they can enclose both the container, in which an aqueous solution of pranoprofen has been sealed, and a deoxygenating agent in such a manner that the outside air is shut off from them. Examples of the container include plastic containers and glass containers, and examples of the sheet include plastic sheets and aluminum sheets. The materials for such containers and sheets may be added with an antioxidant, as exemplified in the above-mentioned Mode II, or may have a low oxygen permeability as discussed below. Also, an antioxidant may be added to an aqueous solution of pranoprofen in Mode III.

The container and the sheet having low oxygen permeability, which are to be used in Mode IV, are preferably made from a

material having an oxygen permeability of not more than 120 cc/m² · 24 hr · atm [20℃ · 90% relative humidity (RH), thickness of material 25 μm], preferably not more than 70 cc/m² · 24 hr · atm (20℃ · 90% RH, thickness of material 25 μm), such as those made from acrylonitrile resins [e.g. acrylonitrile styrene (AS) and acrylonitrile butadiene styrene (ABS)] and polyethy ene terephthalate (PET), with particular preference given to those made from PET.

The solvent to be used to prepare a liquid preparation and an aqueous solution of pranoprofen of the present invention is exemplified by sterile purified water, in particular, distilled water for injection. The concentration of the active ingredient pranoprofen is generally 0.01-2.0 w/v%, preferably 0.05-1.0 w/v%, which is increased or decreased as appropriate according to the object of use.

The antioxidant to be used for the liquid preparation of pranoprofen of the present invention is exemplified by those mentioned for Mode I.

The liquid preparation of the present invention may further contain various additives on demand, such as buffers, isotonizing agents, solubilizing agents, preservatives, thickeners, chelating agents, pH adjusting agents and aromatic agents.

Examples of buffer include phosphate buffer (e.g. sodium dihydrogenphosphate-disodium hydrogenphosphate and potassium dihydrogenphosphate-potassium hydroxide), borate buffer (e.g.

boric acid-sodium tetraborate), citrate buffer (e.g. sodium citrate-sodium hydroxide), tartrate buffer (e.g. tartaric acid-sodium tartrate), acetate buffer (e.g. acetic acid-sodium acetate), carbonate buffer (e.g. sodium carbonate-citric acid and sodium carbonate-boric acid) and amino acid (e.g. sodium glutamate and ε-aminocaproic acid).

When the liquid preparation of pranoprofen is used as an eye drop, it is preferable that borate buffer, acetate buffer or carbonate buffer be used to decrease irritation.

Examples of isotonizing agent include saccharides such as sorbitol, glucose and mannitol, polyhydric alcohols such as glycerol and propylene glycol, salts such as sodium chloride and sodium tetraborate, and boric acid.

Examples of solubilizing agent include non-ionic surfactants such as polyoxyethylenesorbitan monooleate (polysorbate 80), polyoxyethylenemonostearate, polyethylene glycol and polyoxyethylene hydrogenated castor oil.

Examples of preservative include quaternary ammonium salts such as benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, p-hydroxybenzoates such as methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate and butyl p-hydroxybenzoate, benzyl alcohol, phenetyl alcohol, sorbic acid and salts thereof, thimerosal, chlorobutanol and sodium dehydroacetate.

Examples of thickener include polyvinylpyrrolidone, hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose,

hydroxypropylmethylcellulose, carboxymethylcellulose and salts thereof.

Examples of chelating agent include disodium edetate and citric acid.

Examples of pH-adjusting agent include hydrochloric acid, citric acid, phosphoric acid, acetic acid, tartaric acid, sodium hydroxide, potassium hydroxide, sodium carbonate and sodium hydrogencarbonate.

Examples of aromatic agent include 1-menthol, borneol, camphor (e.g. dl-camphor) and eucalyptus oil.

The liquid preparation of the present invention is used as an eye drop, collunarium and the like. When used as an eye drop, its pH is generally adjusted to about 6.0-8.5, preferably about 7.0-8.0, and when used as a collunarium, its pH is generally adjusted to about 6.0-8.5, preferably about 7.0-8.0.

While the method for producing the liquid preparation of the present invention varies depending on the kind of liquid preparation, a known method for each liquid preparation can be used.

The dose of the liquid preparation of the present invention, when used, for example, as an eye drop, is an amount sufficient to effectively resolve ophthalmic inflammation, and varies depending on symptoms and the kind of inflammation. The dose is generally 5.0-1,000 μg/administration, preferably 25-500 μg/administration, which is administered 2 to 5 times a day as appropriate.

The present invention is described in more detail in the following by referring to Experimental Examples and Examples.

Experimental Example 1 [Stability test - No. 1]

A solution of 0.1 w/v% pranoprofen [boric acid, 1.6 w/v%; sodium tetraborate, appropriate amount; disodium edetate, 0.01 w/v%; benzalkonium chloride, 0.005 w/v%; polysorbate 80, 0.1 w/v%; sterile purified water, appropriate amount] was filled in 5 ml polypropylene containers manufactured by adding BHT to 0.05, 0.1 or 0.5 w/v% [oxygen permeability of 25 μm thick test sample, 3,800 cc/m² · 24 hr · atm (20℃ · 90% RH); Gas Permeation Test Method of Plastic Film and Sheet of Japanese Industrial Standards, the equal pressure method [Japanese Standards Association, JIS Handbook, p 400, Tokyo (1991)]] and 15 ml polyethylene terephthalate containers [oxygen permeability of 25 μm thick test samples, 63 cc/m² · 24 hr · atm (20℃ · 90% RH); Gas Permeation Test Method of Plastic Film and Sheet of Japanese Industrial Standards, the equal pressure method [Japanese Standards Association, JIS Handbook, p 400, Tokyo (1991)]], and left standing in the dark at room temperature for 36 months. The residual content of pranoprofen in the containers was determined with time by high performance liquid chromatography. The results are shown in Table 1.

Table 1

Container	Residual content of pranoprofen (%)					
	On preparation	3 months	6 months	12 months	24 months	36 months
PP (control)	100.0	95.6	93.9	-	81.9	78.5
PP-05	100.0	100.4	99.3	99.0	98.5	100.2
PP-01	100.0	100.4	98.3	98.1	95.4	96.0
PP-005	100.0	100.4	98.3	97.0	93.2	93.3
PET	100.0	99.5	101.0	100.3	100.8	99.4

PP : polypropylene container without BHT
oxygen permeability, 3800 cc/m² · 24 hr · atm
(20℃ · 90% RH, 25 μm)

PP-05 : polypropylene container containing 0.5% BHT

PP-01 : polypropylene container containing 0.1% BHT

PP-005: polypropylene container containing 0.05% BHT

PET : polyethylene terephthalate container without BHT
oxygen permeability, 63 cc/m² · 24 hr · atm
(20℃ · 90% RH, 25 μm)

As is evident from Table 1, superior suppression of decomposition of pranoprofen was achieved by preserving pranoprofen in the containers (PP) formed from a mixture containing BHT and in the container (PET) having a low oxygen permeability.

Experimental Example 2 [Stability test - No. 2]

BHT or sodium thiosulfate was added to a basic formulation solution [pranoprofen, 0.1 w/v%; boric acid, 1.6 w/v%; sodium tetraborate, appropriate amount; disodium edetate, 0.01 w/v%; benzalkonium chloride, 0.005 w/v%; polysorbate 80, 0.1 w/v%; sterile purified water, appropriate amount], and the mixture was filled in 5 ml polypropylene containers. The

containers were left standing in the dark at room temperature for 39 months. The residual content of pranoprofen in the containers was determined by high performance liquid chromatography. The results are shown in Table 2.

Table 2

Compound added	Concentration (%)	Residual content of pranoprofen (%)	
		On preparation	after 39 months
Control (not added)	0	100.0	77.0
BHT	0.0004	100.0	99.6
〃	0.0001	100.0	94.7
sodium thiosulfate	0.1	100.0	93.0

As is evident from Table 2, superior suppression of decomposition of pranoprofen was achieved by the addition of respective antioxidants.

Experimental Example 3 [Stability test - No. 3]

BHT, BHA, L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] potassium salt (EPC-K_1), methionine, tryptophan or histidine was added to a basic formulation solution [pranoprofen, 0.05 w/v%; boric acid, 1.6 w/v%; sodium tetraborate, appropriate amount; disodium edetate, 0.01 w/v%; benzalkonium chloride, 0.005 w/v%; polysorbate 80, 0.1 w/v%; sterile purified water, appropriate amount], and the mixture was filled in colorless 15 ml polyethylene terephthalate containers. The containers were left standing under a fluorescent lamp (20 W). When the total irradiation reached

100,000 lux · hr, the residual content of pranoprofen in the containers was determined by high performance liquid chromatography. The results are shown in Table 3.

Table 3

Compound added	Concentration (%)	Residual content of pranoprofen (%)	
		On preparation	after irradiation of 100,000 lux · hr
Control (not added)	0	100.0	52.5
BHT	0.005	100.0	98.0
〃	0.002	100.0	96.6
〃	0.0002	100.0	70.8
BHA	0.002	100.0	92.8
EPC-K_1	0.05	100.0	79.1
〃	0.01	100.0	70.5
〃	0.001	100.0	68.2
methionine	0.24	100.0	95.2
tryptophan	0.06	100.0	96.9
histidine	0.13	100.0	75.9

As is evident from Table 3, the decomposition of pranoprofen caused by the exposure to the light was markedly suppressed by the addition of respective antioxidants.

Experimental Example 4 [Stability test - No. 4]

A solution of 0.1 w/v% pranoprofen [boric acid, 1.6 w/v%; sodium tetraborate, appropriate amount; disodium edetate, 0.01 w/v%; benzalkonium chloride, 0.005 w/v%; polysorbate 80, 0.1 w/v%; sterile purified water, appropriate amount] was filled in 5 ml polypropylene containers and the containers were tightly sealed. The containers were enclosed together with iron oxide (Ageless Z-30, manufactured by Mitsubishi Gas Chemical Company, Inc.) as a deoxygenating agent, with the use of a multi-layer

film of polypropylene/poly(vinyl alcohol)/polyethylene and left standing at room temperature for 30 months. The residual content of pranoprofen in the containers was determined with time by high performance liquid chromatography. The results are shown in Table 4.

Table 4

Enclosing	Residual content of pranoprofen (%)				
	On preparation	2 months	6 months	9 months	30 months
Unenclosed	100.0	95.1	89.4	92.0	80.3
Film-enclosed (deoxygenator)	100.0	98.1	97.6	97.2	101.0
Film-enclosed (N_2 substitution)	100.0	95.0	93.4	89.5	88.5

Containers used: polypropylene containers without BHT

Film: multi-layer film of polypropylene/poly(vinyl alcohol)/polyethylene

deoxygenating agent: iron oxide (Ageless Z-30, manufactured by Mitsubishi Gas Chemical Company, Inc.)

As is evident from Table 4, marked suppression of decomposition of pranoprofen was achieved by sealing a container, in which an aqueous solution of pranoprofen had been sealed, together with a deoxygenating agent.

Example 1 [Eye drop]

(1) Pranoprofen	0.2	g
(2) Disodium hydrogenphosphate	0.5	g
(3) Sodium dihydrogenphosphate	0.1	g
(4) Polyoxyethylene hydrogenated castor oil 60	0.1	g
(5) Poly(vinyl alcohol)	0.2	g

(6)	Sodium chloride	0.8 g
(7)	Benzethonium chloride	0.007 g
(8)	BHT	0.01 g
(9)	Sodium hydroxide	appropriate amount
(10)	Sterile purified water	appropriate amount
	Total	100 ml

(5) was added to about 70 ml of (10) and the mixture was stirred with heating to about 70℃ for dissolution. (4) and (8) were added to this solution and the mixture was admixed until it became a uniform dispersion. The mixture was cooled to room temperature. (1), (2), (3), (6) and (7) were dissolved in this solution and pH was adjusted to 7.2 with (9). (10) was added to make the total amount 100 ml and the mixture was filled in a 5 ml PE container for an eye drop.

Example 2 [Eye drop]

(1)	Pranoprofen	0.4 g
(2)	Sodium chloride	0.5 g
(3)	Polysorbate 80	0.15 g
(4)	Polyethylene glycol	0.5 g
(5)	Citric acid	0.2 g
(6)	Benzalkonium chloride	0.009 g
(7)	Sodium thiosulfate	0.01 g
(8)	Sodium carbonate	appropriate amount
(9)	Sterile purified water	appropriate amount
	Total	100 ml

(1), (2), (3), (4), (5), (6) and (7) were dissolved in

about 70 ml of (9) and pH was adjusted to 8.0 with (8). (9) was added to make the total amount 100 ml and the mixture was filled in a 5 ml PP container for an eye drop.

Example 3 [Eye drop]

(1) Pranoprofen	0.1 g
(2) Potassium dihydrogenphosphate	0.3 g
(3) Conc. glycerol	2.6 g
(4) Potassium hydroxide	appropriate amount
(5) Disodium edetate	0.01 g
(6) EPC-K_1	0.05 g
(7) Methyl p-hydroxybenzoate	0.026 g
(8) Propyl p-hydroxybenzoate	0.014 g
(9) Sterile purified water	appropriate amount
Total	100 ml

About 80 ml of (9) was heated to about 90℃ and (7) and (8) were dissolved. The mixture was cooled to room temperature. An appropriate amount of (4) was dissolved and then, (1), (2), (3), (5) and (6) were dissolved. Its pH was adjusted to 6.5 with (4). (9) was added to make the total amount 100 ml and the mixture was filled in a 10 ml polycarbonate container for an eye drop.

Example 4 [Eye drop]

(1) Pranoprofen	0.1 g
(2) Boric acid	1.6 g
(3) Sodium tetraborate	appropriate amount
(4) Disodium edetate	0.01 g

(5) Polysorbate 80	0.15 g
(6) Benzalkonium chloride	0.007 g
(7) Sterile purified water	appropriate amount
Total	100 ml

(1), (2), (3), (4), (5) and (6) were dissolved in about 80 ml of (7), and pH was adjusted to 7.0 with (3). (7) was added to make the total amount 100 ml and the mixture was filled in a 5 ml PP container for an eye drop, which comprised 0.5% BHT.

Example 5 [Eye drop]

(1) Pranoprofen	0.1 g
(2) Boric acid	1.6 g
(3) Sodium tetraborate	appropriate amount
(4) Disodium edetate	0.01 g
(5) Polysorbate 80	0.15 g
(6) Benzalkonium chloride	0.007 g
(7) Sterile purified water	appropriate amount
Total	100 ml

(1), (2), (3), (4), (5) and (6) were dissolved in about 80 ml of (7), and pH was adjusted to 7.0 with (3). (7) was added to make the total amount 100 ml and the mixture was filled in a 5 ml PP container for an eye drop. The container and iron oxide (Ageless Z-30; manufactured by Mitsubishi Gas Chemical Company, Inc.) were enclosed with a multi-layer film of polypropylene/poly(vinyl alcohol)/polyethylene.

Example 6 [Eye drop]

(1) Pranoprofen	0.05 g

(2) Boric acid	1.6 g
(3) Sodium tetraborate	appropriate amount
(4) Disodium edetate	0.01 g
(5) Benzalkonium chloride	0.005 g
(6) 1-menthol	0.002 g
(7) dl-camphor	0.0005 g
(8) Polysorbate 80	0.1 g
(9) Sterile purified water	appropriate amount
Total	100 ml

(1), (2), (3), (4) and (5) were dissolved in about 70 ml of (9). (6), (7) and (8) were admixed and uniformly dispersed in about 20 ml of (9) heated to about 60℃. This dispersion was added to the above-mentioned solution. The pH of the mixture was adjusted to 7.5 with (3) and (9) was added to make the total amount 100 ml. The mixture was filled in a 15 ml PET container for an eye drop and enclosed to avoid light.

Example 7 [Collunarium]

(1) Pranoprofen	0.4 g
(2) Sodium citrate	0.2 g
(3) Polysorbate 80	0.1 g
(4) Glycerol	2.6 g
(5) Benzethonium chloride	0.007 g
(6) Methionine	0.24 g
(7) Sodium hydroxide	appropriate amount
(8) Sterile purified water	appropriate amount
Total	100 ml

(1), (2), (3), (4), (5) and (6) were dissolved in about 70

ml of (8), and pH was adjusted to 7.5 with (7). (8) was added to make the total amount 100 ml and the mixture was filled in a 5 ml PP container for a collunarium.

Example 8 [Collunarium]

(1) Pranoprofen	1.0	g
(2) Boric acid	1.2	g
(3) Sodium tetraborate	0.8	g
(4) Disodium edetate	0.01	g
(5) Polysorbate 80	0.15	g
(6) Benzalkonium chloride	0.007	g
(7) Sodium hydroxide	appropriate amount	
(8) Sterile purified water	appropriate amount	
Total	100 ml	

(1), (2), (3), (4), (5) and (6) were dissolved in about 80 ml of (8), and pH was adjusted to 7.0 with (7). (8) was added to make the total amount 100 ml and the mixture was filled in a 8 ml PE container for a collunarium. The container and iron oxide (Ageless Z-30; manufactured by Mitsubishi Gas Chemical Company, Inc.) were enclosed with a multi-layer film of polypropylene/poly(vinyl alcohol)/polyethylene.

According to the present invention, the decomposition of the active ingredient pranoprofen is remarkably suppressed. In particular, pranoprofen becomes stable to light, thus permitting long-term preservation of an aqueous solution (preparation) of pranoprofen.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for stabilizing pranoprofen, comprising adding an antioxidant to an aqueous solution of pranoprofen in the presence of a non-ionic surfactant, wherein the antioxidant is at least one compound selected from the group consisting of alkylphenols, benzopyran derivatives, sodium thiosulfate and amino acids.

2. The method for stabilizing pranoprofen according to Claim 1, wherein the weight ratio of the antioxidant to pranoprofen is 0.0002-5.0:1.

3. The method for stabilizing pranoprofen according to Claim 1, wherein the alkylphenol is at least one compound selected from the group consisting of dibutylhydroxytoluene and butylhydroxyanisole.

4. The method for stabilizing pranoprofen according to Claim 1, wherein the benzopyran derivative is at least one compound selected from the group consisting of L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] and salts thereof.

5. The method for stabilizing pranoprofen according to Claim 1, wherein the amino acid is at least one compound selected from the group consisting of methionin, tryptophan and histidine.

6. The stabilizing method according to Claim 1, wherein the aqueous solution of pranoprofen is an eye drop or collunarium.

7. A stable liquid preparation of pranoprofen, comprising pranoprofen and an antioxidant in the presence of a non-ionic surfactant, wherein the antioxidant is at least one compound selected from the group consisting of alkylphenols, benzopyran derivatives, sodium thiosulfate and amino acids.

8. The liquid preparation of Claim 7, wherein the alkylphenol is at least one compound selected from the group consisting of dibutylhydroxytoluene and butylhydroxyanisole.

9. The liquid preparation of Claim 7, wherein the benzopyran derivative is at least one compound selected from the group consisting of L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl-hydrogen phosphate] and salts thereof.

10. The liquid preparation of Claim 7, wherein the amino acid is at least one compound selected from the group consisting of methionin, tryptophan and histidine.

11. The liquid preparation of Claim 7, wherein the weight ratio of the antioxidant to pranoprofen is 0.0002-5.0:1.

12. The liquid preparation of Claim 7, which is an eye drop.

13. The liquid preparation of Claim 7, which is a collunarium.

14. The method for stabilising pranoprofen of claim 1, wherein the non-ionic surfactant is at least one member selected from the group consisting of polyoxyethylenesorbitan monooleate, polyoxyethylene monostearate, polyethylene glycol and polyoxyethylene hydrogenated castor oil.

15. The liquid preparation of pranoprofen of claim 7, wherein the non-ionic surfactant is at least one member selected from the group consisting of polyoxyethylenesorbitan monooleate, polyoxyethylene monostearate, polyethylene glycol and polyoxyethylene hydrogenated castor oil.

16. A stable liquid preparation of pranoprofen according to claim 7 substantially as herein described with reference to any one of the Examples.

Dated this 3rd day of May 1999
SENJU PHARMACEUTICAL CO., LTD.
By their Patent Attorneys
GRIFFITH HACK